IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicant: | H. Lowenheim | Attorney Docket No.: | SOPH116953 |
| Application No.: | 09/622,719 | Group Art Unit: | 1635 |
| Filed: | October 18, 2000 | Examiner: | K.A. Lacourciere |

Title: METHOD FOR THE TREATMENT OF DISEASES OR DISORDERS OF THE INNER EAR

THIRD DECLARATION OF JONATHAN KIL

Seattle, Washington 98101

January 4, 1904

TO THE COMMISSIONER FOR PATENTS:

I, Jonathan Kil, declare as follows:

1. I am the Chief Executive Officer of Sound Pharmaceuticals, Inc., Seattle, Washington, and I am familiar with the subject matter disclosed and claimed in the above-identified application.

2. My colleagues and I conducted the following experiments to assess the effect of a variety of antisense oligonucleotides on the level of expression of $p27^{Kip1}$ mRNA in mouse NIH 3T3 cells cultured *in vitro*.

3. NIH 3T3 cells were transfected with the 14 antisense oligonucleotides shown in Table 1. The antisense oligonucleotides corresponded to portions of the target $p27^{Kip1}$ mRNA. The location of each oligonucleotide is given with reference to the sequence of the mouse $p27^{Kip1}$ cDNA (GenBank accession number U09968; reported in Polyak,K., et al, *Cell* **78:** 56-66 (1994)). Antisense oligonucleotides SPI5114 and SPI5116 have identical nucleic acid sequences, but SPI5116 includes both phosphothioate and 2" MOE backbone linkages.

Table 1

| Oligonucleotide Name | Oligonucleotide Sequence | Location of Oligonucleotide |
|---|---|---|
| SPI5101 | TGGCTCTCCTGCGCC | 306-320 |

Attachment A

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| Oligonucleotide Name | Oligonucleotide Sequence | Location of Oligonucleotide |
|---|---|---|
| SPI5108 | CATCCTGGCTCTCCTGCGCCAGCAC | 301-325 |
| SPI5114 | CCGCTGACATCCTGGCTCTCCTGCG | 308-332 |
| SPI5116 | CCGCTGACATCCTGGCTCTCCTGCG | 308-332 |
| SPI5906 | TCTCACGTTTGACAT | 1-15 |
| SPI5907 | ATTCCACTTGCGCTG | 169-183 |
| SPI5908 | TCTCCACCTCCTGCC | 227-241 |
| SPI5501 | TGCTCCGCTAACCC | 247-440 |
| SPI5505 | GACACTGCTCCGCTAACCCAGCCTG | 421-445 |
| SPI5517 | GACACTGCTCCGCTAACCCAG | 425-445 |
| SPI5518 | CTGCTCCGCTAACCCAGCCTG | 421-441 |
| SPI5519 | CACTGCTCCGCTAACCCAGCC | 423-443 |
| SPI5801 | CATCCGCTCCAGGCT | 34-48 |
| SPI5806 | CGTCCATCCGCTCCAGGCTCG | 32-52 |

The cells were incubated in the presence of the oligonucleotide for 26 hours. Real time RT-PCR was used to measure the amount of $p27^{Kip1}$ mRNA present in total RNA extracted from the treated cells.

4. Enclosed herewith as Attachment B is a graph showing the level of $p27^{Kip1}$ mRNA in the cells treated with the different oligonucleotides, compared to the control level of $p27^{Kip1}$ mRNA in cells treated with the Lipofectamine lipid delivery vehicle without oligonucleotides. The results shown in the graph demonstrate that all of the tested oligonucleotides caused a significant reduction in the level of $p27^{Kip1}$ mRNA in the treated cells.

5. All statements made herein and of my own knowledge are true, and all statements made on information and belief are believed to be true; and further, these statements were made

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with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the above-identified application or any patent issued thereon.

Respectfully submitted,

Jonathan Kil, M.D.

Date: 12/27/04

BFM:tmm

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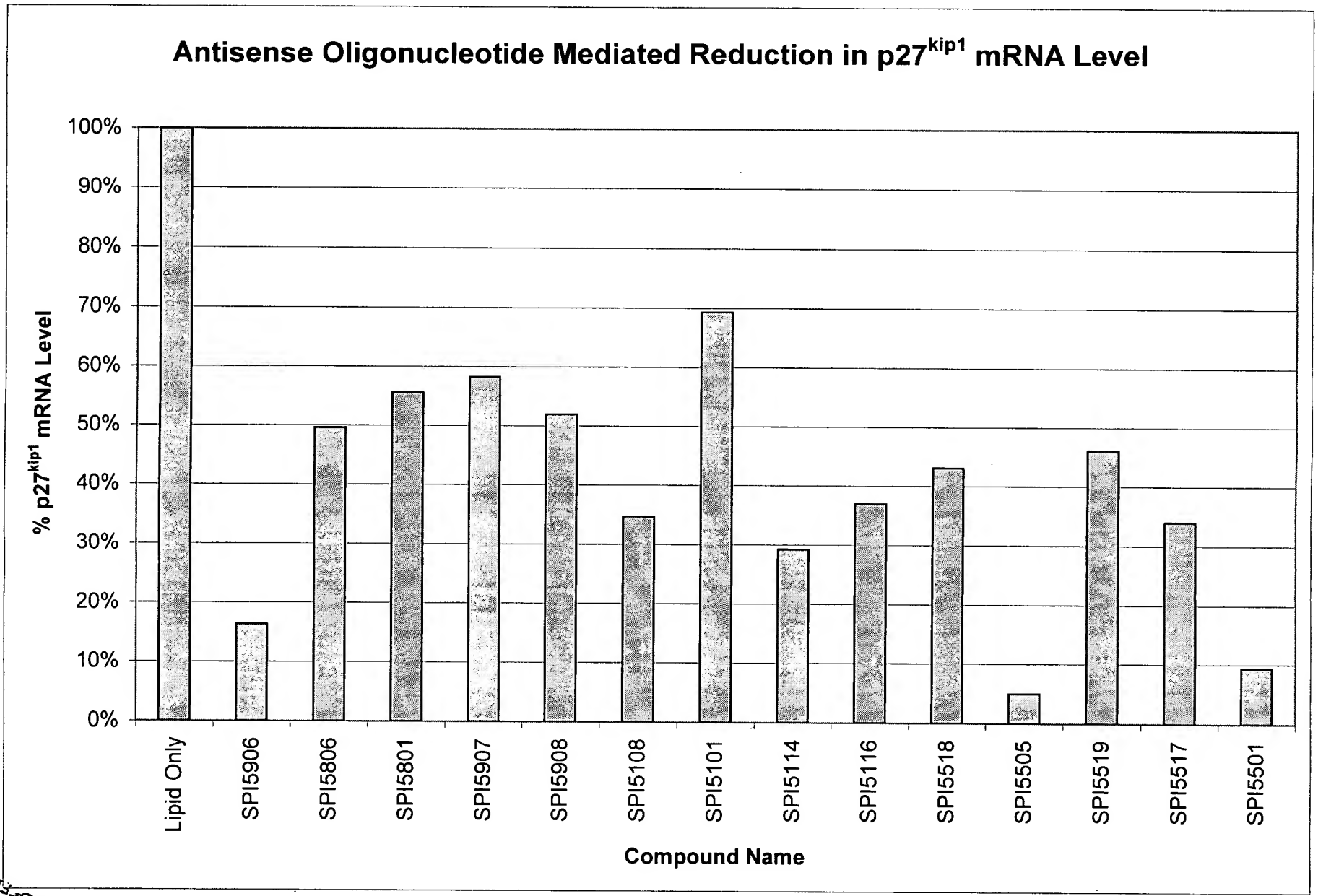




Attachment B